Bradford Hill's Criteria for Causation Applied to LDL Cholesterol and Coronary Heart Disease

Review of literature for book chapter VAT-TRAP E.Leatham 2025

Introduction

The relationship between elevated low-density lipoprotein cholesterol (LDL-C) and coronary heart disease (CHD) is one of the most intensively studied topics in cardiovascular medicine. However, establishing causality requires more than statistical association. Sir Austin Bradford Hill's classic 1965 framework for causal inference remains an enduring guide for evaluating whether an observed association is likely causal or coincidental (1).

Applying Hill's nine aspects of association to the LDL hypothesis provides a structured way to test whether elevated LDL-C is indeed a **cause** of CHD. Below, each criterion is discussed, with supporting and opposing evidence from epidemiology, clinical trials, and molecular biology.

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1. Strength of Association

Hill's first criterion is the *strength* of the observed relationship. Large prospective cohort studies such as Framingham, ARIC, and MESA demonstrate that individuals with higher LDL-C levels have a significantly greater risk of myocardial infarction and CHD mortality, even after adjusting for confounding factors (2,3).

Meta-analyses indicate that each 1 mmol/L increase in LDL-C confers a roughly 30–40% increase in CHD risk (3). These findings are consistent across genders and ethnicities.

However, critics such as Ravnskov et al. argue that the magnitude of the association is modest, with relative risks generally below 3, and that in older populations, the relationship may even invert (4,5). They suggest that confounding or reverse causation may weaken the apparent causal strength.

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2. Consistency

Consistency implies that the association is observed repeatedly, in different populations, at different times, and under varying conditions.

Epidemiological data spanning several decades demonstrate a reproducible link between LDL-C and CHD risk across continents (2,3). Genetic studies and randomized controlled trials (RCTs) also replicate the association, reinforcing its stability.

Yet, Ravnskov's meta-analysis of elderly cohorts reported inverse or null relationships between LDL and mortality (5), suggesting that in specific groups, reverse causation (where illness lowers cholesterol) may distort the association. More recent evidence from a large Danish prospective cohort (BMJ 2020) failed to reproduce these inverse associations in older adults, showing instead a graded, positive relationship between LDL-C and both all-cause and cardiovascular mortality. When early deaths and comorbidity were accounted for, the apparent protective effect of higher LDL largely disappeared, supporting reverse causation as the explanation for earlier contradictory findings (6).

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3. Specificity

In Hill's model, a cause–effect relationship is stronger if one exposure leads to one specific disease. Elevated LDL-C is not entirely specific, as it contributes to atherosclerosis in multiple vascular beds (carotid, peripheral, and cerebral). However, its most characteristic manifestation is coronary plaque formation (2,3).

In modern epidemiology, specificity is not considered essential; many exposures (e.g. smoking) have multiple disease outcomes.

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4. Temporality

For causation, exposure must precede disease. In prospective studies, elevated LDL-C levels are measured long before coronary events occur (3). Mendelian randomization (MR) studies—where inherited variants cause lifelong differences in LDL—demonstrate that higher lifelong LDL exposure precedes CHD development (2).

RCTs of statins, ezetimibe, and PCSK9 inhibitors show that lowering LDL before clinical events reduces those events (2). Temporality is therefore firmly satisfied.

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5. Biological Gradient (Dose–Response Relationship)

The biological gradient refers to increasing risk with increasing exposure. Observational cohorts consistently show that CHD risk rises in step with LDL-C (2,3). Furthermore, in clinical trials, greater LDL-C reductions yield larger proportional risk reductions in CHD events (2).

For example, the Cholesterol Treatment Trialists' meta-analysis showed that each 1 mmol/L reduction in LDL-C yields roughly a 22% reduction in major vascular events (7). Mendelian randomization data reveal that people with lifelong lower LDL-C due to PCSK9 or LDLR variants have proportionally lower CHD risk (8).

Although some critics argue that the relationship is not perfectly linear (5), the overall gradient is clear and reproducible.

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6. Plausibility (Mechanistic Explanation)

LDL-C has a well-defined pathophysiological mechanism. LDL particles infiltrate the arterial intima, undergo oxidative modification, and are taken up by macrophages to form foam cells, initiating an inflammatory cascade that leads to plaque formation .

Familial hypercholesterolaemia (FH), caused by LDL receptor or apoB mutations, leads to extremely high LDL-C levels and premature coronary disease (2,3). Conversely, therapies that enhance LDL clearance markedly reduce CHD incidence.

These findings fulfil Hill's criterion of biological plausibility.

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7. Coherence

Coherence demands that the proposed causal relationship not contradict current biological or epidemiologic knowledge. The LDL hypothesis is coherent with known pathology: atherosclerotic plaques contain abundant cholesterol and LDL-derived lipids (2).

Autopsy and intravascular imaging confirm that lipid-rich plaques correspond to the sites of rupture in myocardial infarction. The hypothesis integrates seamlessly with existing models of inflammation, endothelial dysfunction, and thrombosis.

Critics, however, note that in late life or chronic illness, low LDL may coincide with poor outcomes, suggesting that very low cholesterol can mark frailty rather than health (5). Such findings reflect context-specific biology rather than incoherence.

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8. Experiment

The experimental criterion is the most powerful. Randomized controlled trials of LDL-lowering therapies provide direct evidence that reducing LDL reduces CHD events.

- **Statins:** Dozens of large-scale trials (e.g. 4S(9), HPS(10), JUPITER (11,12)) show consistent reductions in myocardial infarction, revascularization, and CHD mortality proportional to LDL reduction.
- **Ezetimibe (IMPROVE-IT** (13)**)** and **PCSK9 inhibitors (FOURIER** (14)**, ODYSSEY, VESALIUS-CV** (15)**)** further confirm causality by demonstrating that additional LDL lowering beyond statins yields further event reductions.
- **Mendelian randomization studies**—"nature's randomized trials"—show that genetic variants lowering LDL over a lifetime confer protection against CHD of similar magnitude per mmol/L LDL reduction (16).

Thus, experimental and genetic evidence align to fulfil Hill's most decisive criterion.

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9. Analogy

Analogy considers whether similar exposures produce similar outcomes. Other atherogenic lipoproteins (e.g. remnant cholesterol, lipoprotein(a)) are causally linked to CHD(17). Familial hypercholesterolaemia provides a natural analogy: extreme lifelong LDL elevation causes early-onset coronary atherosclerosis. Lowering LDL in these patients reverses or prevents events (18)

Integration of the Evidence

When all nine criteria are evaluated, the LDL–CHD relationship satisfies nearly all. The **experiment** and **plausibility** criteria are particularly strong. The coherence of evidence—from cell biology to randomized trials—makes LDL a paradigmatic example of causal inference in medicine.

Critics such as Ravnskov et al (4) challenge the interpretation, citing studies where LDL fails to predict CHD in older adults, or where statin benefits may stem from anti-inflammatory rather than lipid effects. However, the *totality of evidence*—including genetic and

interventional data—makes the LDL hypothesis among the most robust causal models in modern epidemiology.

Conclusion

Applying Bradford Hill's framework to the LDL–CHD hypothesis leads to a compelling conclusion: elevated LDL-C is a **direct causal factor** in atherosclerotic coronary disease. The relationship is biologically plausible, consistent across methodologies, supported by genetic and pharmacologic experiments, and coherent with established cardiovascular pathology.

While alternative mechanisms and modifiers exist, the causal role of LDL in CHD remains one of the best-substantiated findings in medical science.

References

1. Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med [Internet]. 1965 May [cited 2025 Dec 4];58(5):295–300. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC1898525/

2. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J [Internet]. 2017 Aug 21 [cited 2025 Dec 4];38(32):2459–72. Available from: https://doi.org/10.1093/eurheartj/ehx144

3. Schade DS, Helitzer D, Eaton P. Evidence that Low Density Lipoprotein Is the Primary Cause of Atherosclerotic Cardiovascular Disease: A Bradford-Hill Approach. World J Cardiovasc Dis [Internet]. 2017 Sept 19 [cited 2025 Dec 4];7(9):271–84. Available from: https://www.scirp.org/journal/paperinformation?paperid=79174

4. Ravnskov U, de Lorgeril M, Diamond DM, Hama R, Hamazaki T, Hammarskjöld B, et al. LDL-C does not cause cardiovascular disease: a comprehensive review of the current literature. Expert Rev Clin Pharmacol [Internet]. 2018 Oct 3 [cited 2025 Dec 4];11(10):959–70. Available from: https://doi.org/10.1080/17512433.2018.1519391

5. Ravnskov U, Diamond DM, Hama R, Hamazaki T, Hammarskjöld B, Hynes N, et al. Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. 2016 June 1 [cited 2025 Dec 4]; Available from: https://bmjopen.bmj.com/content/6/6/e010401

6. Johannesen CDL, Langsted A, Mortensen MB, Nordestgaard BG. Association between low density lipoprotein and all cause and cause specific mortality in Denmark:

prospective cohort study. 2020 Dec 8 [cited 2025 Dec 4]; Available from: https://www.bmj.com/content/371/bmj.m4266

7. Collaboration CTT (CTT). Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet [Internet]. 2010 Nov 13 [cited 2025 Dec 4];376(9753):1670–81. Available from: https://www.thelancet.com/article/S0140-6736(10)61350-5/fulltext

8. Burgess S, Harshfield E. Mendelian randomization to assess causal effects of blood lipids on coronary heart disease: lessons from the past and applications to the future. Curr Opin Endocrinol Diabetes Obes [Internet]. 2016 Apr [cited 2025 Dec 4];23(2):124–30. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4816855/

9. Group SSSS. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). The Lancet [Internet]. 1994 Nov 19 [cited 2025 Dec 4];344(8934):1383–9. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(94)90566-5/fulltext

10. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg [Internet]. 2007 Apr 1 [cited 2025 Dec 4];45(4):645-654.e1. Available from: https://www.jvascsurg.org/article/S0741-5214(07)00003-1/fulltext

11. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, et al. Effect of Two Intensive Statin Regimens on Progression of Coronary Disease. N Engl J Med [Internet]. 2011 Dec 1 [cited 2025 Dec 4];365(22):2078–87. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1110874

12. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N Engl J Med [Internet]. 2008 Nov 20 [cited 2025 Dec 4];359(21):2195–207. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa0807646

13. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med [Internet]. 2015 June 18 [cited 2025 Dec 4];372(25):2387–97. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1410489

14. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med [Internet]. 2017 May 4 [cited 2025 Dec 4];376(18):1713–22. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1615664

15. Bohula EA, Marston NA, Bhatia AK, Ferrari GMD, Leiter LA, Nicolau JC, et al. Evolocumab in Patients without a Previous Myocardial Infarction or Stroke. N Engl J Med [Internet]. [cited 2025 Dec 4];0(0). Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2514428

16. Ference BA. Mendelian randomization studies: using naturally randomized genetic data to fill evidence gaps. Curr Opin Lipidol [Internet]. 2015 Dec [cited 2025 Dec 4];26(6):566. Available from:

https://journals.lww.com/co-lipidology/fulltext/2015/12000/mendelian_randomization_studies__using_naturally.12.aspx

17. Doherty S, Hernandez S, Rikhi R, Mirzai S, De Los Reyes C, McIntosh S, et al. Lipoprotein(a) as a Causal Risk Factor for Cardiovascular Disease. Curr Cardiovasc Risk Rep [Internet]. 2025 [cited 2025 Dec 4];19(1):8. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11836235/

18. Langslet G, Holven KB, Bogsrud MP. Treatment goals in familial hypercholesterolaemia—time to consider low-density lipoprotein-cholesterol burden. Eur J Prev Cardiol [Internet]. 2022 Nov 23 [cited 2025 Dec 4];29(17):2278–80. Available from: https://doi.org/10.1093/eurjpc/zwab228